FDA RECOMMENDATIONS FOR CLINICAL TRIALS of FACTOR VIII PRODUCTS: CURRENT THINKING

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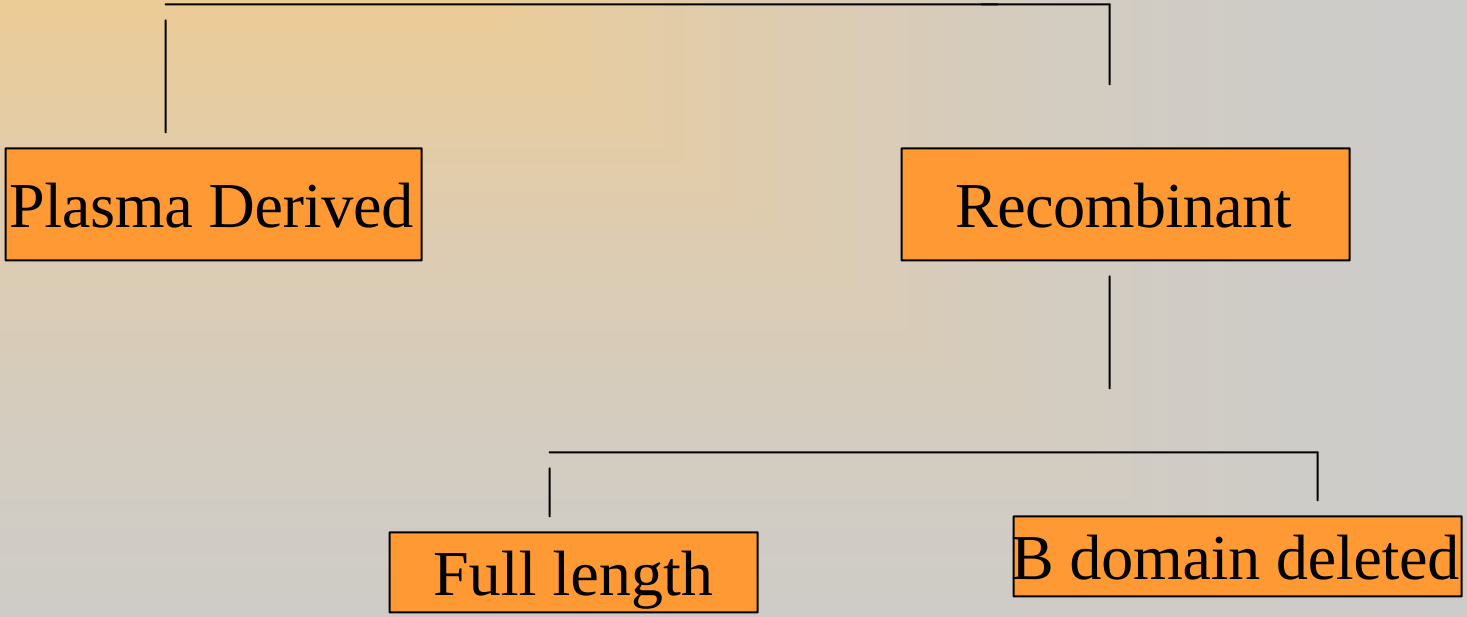
Outline

- Clinical design of the products approved, to date
- Types of clinical trial for approval of new product: FDA's Past and Present thinking and how our thinking evolved with respect to:
  - Clinical Trial designs to support efficacy
  - Clinical trial designs to support safety of the product: immunogenicity

Licensed Products



- Plasma Derived
  - Hemofil M
  - Monoclate P
  - Monarc M
  - Humate P
  - Alphanate
- Recombinant
  - Kogenate (Helixate)
  - Kogenate FS
  - Recombinate
  - ReFacto
  - Advate

Clinical trials for plasma derived Factor VIII products

- Licensed (1960's) based on PK studies.
  - Half life of these products ranged from 14- 16hrs
- In the 1980's, all plasma derived factor VIII products underwent major manufacturing change:
  - Purification step
  - Viral inactivation step/s
    - Comparative PK against the old product
    - Safety study for inhibitor formation
      - No pre licensure requirement on number of subjects or exposure days.
      - All information on immunogenicity was obtained post marketing

- Heat treatment as viral inactivation step (1997)
  - Post marketing phase IV safety study was required to monitor the rate of new inhibitors in PTP
    - Sample size of 50
    - Exposure duration –two years
    - Safety endpoint:
      - Assuming the maximum bi annual rate of observed inhibitor incidence of 3% , the one sided 95% CI for this incidence with a sample size of 50 is 0-7.3%. With a sample size of 50 evaluable patients monitored for two years , if more than three patients developed inhibitors with a titer higher than 0.7 BU that persist a month the incidence will be deemed higher than that of any licensed products at that time.

Recombinant Factor VIII Products

Trials for initial licensure (early 1990's)

- Comparative PK against licensed plasma derived
- Efficacy studies for treatment of bleeding episodes and surgical prophylaxis originally in PUPs but later modified to include PTPs
- With early products safety data on immunogenicity was collected mostly post-marketing, with minimum requirement prelicensure

Recombinant products with manufacturing changes

- Major manufacturing changes (late 1990's)
  - comparative PK with the predecessor product

    Efficacy studies for treatment of bleeding episodes and surgical prophylaxis in both PUPs and PTP

- Safety study in PTPs
  - PUP's studies were not required but were replaced with pediatric studies
  - Information on immunogenicity must be available prior to licensure
  - Safety endpoint
  - # of subjects to be at least 80 previously-treated patients (PTPs) followed not less than 50 exposure days for development of all types of inhibitors

Safety trials for recombinant products with major manufacturing changes

- If 80 subjects are evaluated for 50 exposure days and none of them develops an inhibitor, that outcome enables one to rule out, with a 95% confidence, a frequency of true inhibitor rate $\geq$4%
  - If one patient out of 80 developed a inhibitor then it rules out with a 95% CI a rate of 5.6%
  - If 2 patients out of 80 developed an inhibitor then the true inhibitor incidence (upper bound CI) may be as high as 8.47% which is judged clinically unacceptable

Incidence of inhibitors in IND studies for recombinant products

Products	#of pts inhibitors/#exposed(%)	Follow up for # of exposure days	Two sided C.I	Types of inhibitors (High vs Low)	Def of Positive Inhibitor
Advate	1/103= 0.9%	>75 days	0.02%, 5.29%	low	1BU
ReFacto	1/113= 0.9%	>50 days	.02%, 4.83%	high	0.6BU
Recombinant	0/142= 0%	>70 days	0,2.56%		

Current thinking (2002- 2003)

- New Product
  - New molecular entity
  - Manufacturing change of an existing licensed product
  - Indication sought
    - Control and prevent hemorrhagic episodes in patients with hemophilia A
    - For surgical prophylaxis in patients with hemophilia A

Trials to support licensure

- Comparative PK study
  - licensed Plasma derived against the product
    - The 90% confidence intervals for the ratio of the test product over the reference product for the primary PK parameters should fall within the interval (0.80, 1.25).

    -Recovery before and after 50 exposure days for efficacy and safety study

Trials to support licensure: Efficacy study

- Supportive efficacy studies for licensure
  - PTP
    - Treatment of a bleeding episode
    - Surgical prophylaxis
  - No PUPs study required
  - Efficacy/PK studies in pediatric population
    - Post licensure
    - Protocol to be submitted and approved prior to licensure

Trials to support licensure: Safety Study

- PTP
  - Heavily pretreated (> 150 exposure days)
  - no previous history of inhibitors
  - Immunocompetent
  - Inhibitors
    - Sponsors responsible to clearly defined in the protocol
      - Low /high
      - Cut off value
      - Assay
      - Confirmation of the positive titers
    - All inhibitors (high or low) analyzed as intent to treat for primary safety analysis

- Safety study
  - Acceptable safety endpoint
    - Sample size 80 subjects
    - Exposure days minimum of 50 exposure days
    - To rule out 6.8% (as the upper bound of the 2-sided 95% confidence interval) for the rate of all inhibitor incidence, by intent to treat analysis

Post Marketing Studies

- Additional indications
  - Continuous infusion
  - Routine prophylaxis
- Pharmaco-vigilance registry